PB88-161909

Health and Environmental Effects Profile for 2-Phenylphenol

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84

US Department of Commerce
National Technical Information Service

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-84/334	2.	3. RECIPIENT'S ACCESSION NO. PB88 161989/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for 2-Phenylphenol		5. REPORT DATE January 1984
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The Health and Environmental Effects Profile for 2-phenylphenol was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 2-Phenylphenol has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for 2-phenylphenol is 1.9×10^{-3} (mg/kg bw/day)$^{-1}$ for oral exposure.

.0019

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Public	Unclassified	67
	20. SECURITY CLASS (This page) Unclassified	22. PRICE PC14.95/MF6.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-161989

EPA/600/X-84/334
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 2-PHENYLPHENOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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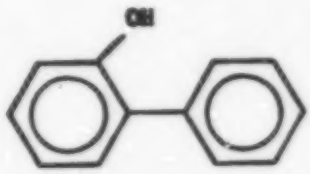
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BUN	Blood urea nitrogen
bw	Body weight
DNA	Deoxyribonucleic acid
GC	Gas chromatography
HPLC	High pressure liquid chromatography
LD_{50}	Dose lethal to 50% of recipients
MS	Mass spectrometry
MTD	Maximum tolerated dose
ppb	Parts per billion
ppm	Parts per million
SCE	Sister chromatid exchange
w/w	Wet weight? (See Chapter 7)

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

2-Phenylphenol is a common chemical synonym for the compound currently known in Chemical Abstract usage as (1,1'-biphenyl)-2-ol. Other chemical synonyms include 2-hydroxydiphenyl, 2-biphenylol, ortho-phenylphenol, orthoxenol and ortho-hydroxybiphenyl. It is known by the trade name "Dowcide 1" (BCPC, 1977). The structure and molecular formula for 2-phenylphenol are as follows:



Empirical formula: $C_{12}H_{10}O$

Molecular weight: 170.22

The Chemical Abstracts Service (CAS) Registry number is 90-43-7.

1.2. CHEMICAL AND PHYSICAL PROPERTIES

2-Phenylphenol is a white crystalline solid with a mild odor at room temperatures. Selected physical properties are listed below (BCPC, 1977; Verschueren, 1983, unless otherwise stated):

Specific gravity:	1.217 at 25/25°C
Melting point:	56-57°C
Boiling point:	275-286°C

Vapor pressure (Perry and Chilton, 1973):	Temp. °C	mm Hg
	100	1.0
	131.6	5.0
	146.2	10.0
	163.3	20.0
Water solubility:	700 mg/ℓ (ppm)	
BCF: (calculated from water solubility)	15 (Kenaga, 1980)	
Soil sorption coefficient: (calculated from water solubility)	120 (Kenaga, 1980)	

2-Phenylphenol is soluble in most organic solvents. It forms 2-phenylphenates with alkali metals such as sodium (BCPC, 1977).

1.3. PRODUCTION DATA

2-Phenylphenol has been manufactured as a by-product in the hydrolysis of monochlorobenzene with aqueous sodium hydroxide (Reed, 1978; Weaver et al., 1979). Current domestic production may be deliberate, using the above synthesis route. Reed (1978) has suggested that the by-product route is becoming obsolete and that the compound is being made by the dehydrogenation of 2-cyclohexylidene-cyclohexanone produced by the base catalyzed dimerization of cyclohexanone.

Currently, the only domestic producer of 2-phenylphenol (or its sodium salt) is Dow Chemical Co. in Midland, MI (SRI, 1983; USITC, 1983a). The only available production figure is for 1977, when between 1 and 10 million pounds were produced (U.S. EPA, 1980a). In 1982, 50,000 pounds of 2-phenylphenol were imported into the United States (USITC, 1983b).

1.4. USE DATA

In 1978, 2.2 million kg of 2-phenylphenol and its sodium salt were used in various applications in the United States (Trotz and Pitts, 1981). The sodium salt is made by reacting 2-phenylphenol with sodium hydroxide. 2-Phenylphenol is used as an industrial antimicrobial agent with applications in hard-surface cleaners, metalworking fluids, automotive gaskets, leathers, paints and polish formulating (Trotz and Pitts, 1981). 2-Phenylphenol plus xylenols or pine oil are used as antiseptics-disinfectants in two versions of Lysol® cleaners made by Lehn and Fink (Gump, 1979). Also as a microbial agent, 2-phenylphenol has applications as a preservative for cellulosic materials such as timber and paper (Reed, 1978). Additionally, 2-phenylphenol is used commercially as a dye carrier for polyester fibers (Reed, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

Pertinent data regarding hydrolysis of 2-phenylphenol were not found in the available literature cited in the Appendices. However, the chemical structure of 2-phenylphenol indicates that hydrolysis is not likely to be of environmental significance. In regard to chemical reactions in the aquatic environment, Onodera et al. (1981, 1983) have shown that under laboratory conditions simulating wastewater treatment, dilute aqueous solutions of 2-phenylphenol react with hypochlorite to form chlorophenylphenol (which is then degraded to other products); this reaction is dependent upon the pH of the solution. Actual occurrence of 2-phenylphenol chlorination during wastewater chlorination treatments has not been investigated; however, it is unlikely that this process is significant in the environmental loss of 2-phenylphenol.

The environmental fate of 2-phenylphenol due to photolysis has not been investigated adequately. Coulangeon et al. (1980) prepared aqueous solutions of 2-phenylphenol and then irradiated them with a 296 nm light source. Solutions with pH 0-1 and pH 1-10 displayed an absorption maximum of 282 nm, while solution with pH 10-14 displayed an absorption maximum of 310 nm. These results indicate that 2-phenylphenol can absorb radiation under environmental conditions, but more data are required to predict photolysis rates and significance.

The ability of 2-phenylphenol to undergo microbial degradation has been studied by several investigators. Using activated sludge from a communal clarification plant, Pauli and Franke (1971) found, in the laboratory, that 2-phenylphenol was degraded rapidly; at doses of 30 and 100 mg/ℓ, 100% of the 2-phenylphenol was degraded within 3 days. Garrison and Hill (1972) exposed 2-phenylphenol to aerated mixed cultures of aerobic microorganisms;

from an initial concentration of 50 ppm, the 2-phenylphenol concentration fell to 25 ppm in ~145 hours. However, some of the loss was attributable to volatilization. Results of Voets et al. (1976) indicate that 2-phenylphenol is degraded easily in the aquatic environment; after 3 weeks of application of 10-40 mg/ℓ at 22°C, 100% of the 2-phenylphenol underwent degradation during both aerobic and anaerobic conditions with synthetic sewage. In addition, Voets et al. (1976) identified two microbial strains, Pseudomonas sp. and Alcaligenes sp., capable of using 2-phenylphenol as a sole carbon and energy source. Ahmed and Focht (1972) have shown that two species of Achromobacter, as isolated from sewage effluent using biphenyl and chlorobiphenyl, are capable of degrading 2-phenylphenol. In an abstract of an Italian study, Maggio et al. (1976) reported that the biodegradation rate of 2-phenylphenol depends upon the type of inoculum used and does not depend upon excess oxygen or BOD. Reichardt et al. (1981) found 2-phenylphenol to be a degradation product from the microbial breakdown of biphenyl.

The transport of 2-phenylphenol from water via volatilization has been studied by Garrison and Hill (1972) under laboratory conditions. From an initial concentration in distilled water of 100 mg/ℓ, 57 mg/ℓ remained after 54 hours in an aerated solution, while 80 mg/ℓ remained after 168 hours in a nonaerated solution. Thus, volatilization from water is likely to be environmentally significant, although the rates have not been investigated adequately.

Kenaga (1980) has calculated a BCF of 15 for 2-phenylphenol from its water solubility. A BCF >1000 indicates that the compound is likely to be strongly bioconcentrated, while a factor <100 indicates that the compound is unlikely to have significant bioconcentration. Also, the soil sorption coefficient, as predicted by Kenaga (1980) (Section 2.3.), indicates that

2-phenylphenol is not strongly bound to soil matter; therefore, sorption onto suspended particulate matter in water and subsequent sedimentation is probably environmentally significant, although this possibility has not been experimentally demonstrated.

The overall persistence of 2-phenylphenol in the aquatic environment has not been adequately determined. Using laboratory studies, Garrison and Hill (1972) concluded that 2-phenylphenol and other dye carriers are persistent enough to become water pollutants after passing through quiescent or aerated lagoons. The microbial degradation rates noted earlier indicate that 2-phenylphenol can be degraded completely within a matter of days under proper conditions.

2.2. AIR

Specific data regarding the fate or transport of 2-phenylphenol in the atmosphere were not located in the available literature cited in the Appendices. The available photolysis data are not helpful in predicting photodecomposition or lack of it. It has been suggested by Cupitt (1980) that adsorption will be a reasonable vapor-phase removal mechanism only for chemicals with saturation vapor pressures of $\leq 10^{-7}$ mm Hg. The vapor pressure of 2-phenylphenol is several orders of magnitude higher than 10^{-7} mm Hg; therefore, sorption in the air is not likely.

2.3. SOIL

The environmental fate and transport of 2-phenylphenol in the soil has not been adequately investigated. Data specific to any of the fate and transport processes is minimal; however, it appears possible that microbial degradation is the major removal mechanism for 2-phenylphenol from soil.

As noted in Section 2.1., chemical hydrolysis of 2-phenylphenol in the environment appears unlikely and photolysis is uncertain.

Chambers et al. (1963) and Tabak et al. (1964) have shown that 2-phenylphenol is degraded by phenol-adapted bacteria. The adapted bacteria were obtained from garden soil, compost, river mud and sediment from a waste lagoon of a petroleum refinery. In the laboratory, the adapted bacteria cultures degraded 2-phenylphenol (100 ppm) in 3-6 days. The genera found to be able to degrade 2-phenylphenol included Pseudomonas, Achromobacter and Flavobacterium. The microbial degradation data presented in Section 2.1. indicate that 2-phenylphenol can be degraded readily by microorganisms. Therefore, it appears likely that microbial degradation of 2-phenylphenol in the soil is environmentally significant.

Pertinent data regarding volatilization of 2-phenylphenol from soil were not found in the available literature. Volatilization from water is discussed in Section 2.1.

Kenaga (1980) has predicted a soil sorption coefficient of 120 for 2-phenylphenol using its water solubility. Compounds having a value of ~1000 are bound tightly to organic matter in soil and are considered immobile; those <100 are moderately to highly mobile. The value for 2-phenylphenol predicts that it is neither immobile nor highly mobile. Experimental data regarding 2-phenylphenol leaching in the soil were not located in the available literature.

Data regarding the overall persistence of 2-phenylphenol in the soil were not located in the available literature cited in the Appendices.

3. EXPOSURE

3.1. WATER

Sheldon and Hites (1978) detected phenylphenol at a concentration of 0.3 ppb in the Delaware River in March, 1977, but the isomer was not determined; it was not detected in August, 1976, by Sheldon and Hites (1978) or in August, 1977, by Hites (1979) in the Delaware River.

Tomson et al. (1981) have detected 2-phenylphenol levels of $\leq$0.008 µg/ℓ in sewage samples taken in Phoenix, AZ, but it was undetected in groundwater samples following a rapid infiltration method of sewage treatment. Collins (1976) detected 2-phenylphenol in effluent and sludge from a Putnam, CT, water treatment plant. 2-Phenylphenol has been detected in effluents from two of five United States leather tanning plants in 1978 (Thruston and McGuire, 1981), and in raw wastes from a textile finishing plant that used it as a dye carrier (Gordon and Gordon, 1981).

2-Phenylphenol has been detected in surface and groundwaters in England (Fielding et al., 1981; Waggot, 1981; Richardson, 1981), Italy (Sanna et al., 1983) and Japan (Akiyama et al., 1980; Koga et al., 1979). In Australia, it was detected in groundwater apparently polluted from wastes being dumped in quarry holes (Stepan et al., 1981). A 4-year study in West Germany found 2-phenylphenol levels of 0.1-10 µg/ℓ in water from a water filtration plant, <1-95 µg/ℓ in sanitaria wastewater, <0.1-1 µg/ℓ in the Ruhr River and 0.02µ g/ℓin drinking water (Dietz and Traud, 1978).

The U.S. EPA STORET data base (see Appendix A) has no reports for 2-phenylphenol.

3.2. FOOD

In the Total Diet Program conducted by the FDA, ready-to-eat foods were collected as market basket samples from retail stores in up to 30 American cities annually and were analyzed for pesticide residue levels in the total adult diet; the results of this program with respect to 2-phenylphenol are summarized in Table 3-1. From June, 1969 through July, 1976, 2250 food composites were analyzed for 2-phenylphenol residues with 27 positive detections, of which 15 were trace amounts (<0.001 ppm). The quantifiable residue range was from 0.05-0.40 ppm, with most residues detected in fruit food classes (see Table 3-1). In addition to the Total Diet Program for adults, the FDA monitored infant and toddler diet samples for pesticide residues in the final 2 years of the program. For the testing period August, 1975 to July, 1976, a trace level of 2-phenylphenol was found in one sample of the toddler diet from the fruit and fruit juice food class (Johnson et al., 1981a).

Duggan et al. (1983) have compiled data concerning pesticide residue levels in United States' foods from the following three sources: the Total Diet Program (discussed above), FDA's Monitoring Program for raw agricultural commodities (both domestic and imported), and the USDA National Residue Program, administered by the Food Safety and Inspection Service, concerning red meats and poultry. With respect to 2-phenylphenol, Duggan et al. (1983) reported that the 1971-1976 average dietary intake was calculated to be 0.00003 mg/kg bw/day as compared with the WHO/FAO ADI level of 1.0 mg/kg bw/day. 2-Phenylphenol was found infrequently in fish and shellfish (1 positive sample during fiscal years 1970-1976), in leaf and stem vegetables (10 positive samples during 1973-1975), and in vine and ear vegetables (5 positive samples in 1970 only). Duggan et al. (1983) summarized the

TABLE 3-1

2-Phenylphenol Residues in Adult Total Diet Samples*

Testing Period	No. of Food Composites Analyzed	No. of Composites with Residues	No. of Composites with Residues Reported as Trace	Range (ppm)	Food Class (No. of Positive Residues/Range, ppm)
August 1975-July 1976	240	1	1	T	sugar and adjuncts (1) (T)
August 1974-July 1975	240	2	1	0.20	garden fruits (1) (T) fruits (1) (0.20)
August 1973-July 1974	360	5	2	0.05-0.20	fruits (4) (0.05-0.20) sugar and adjuncts (1) (T)
August 1972-July 1973	360	1	1	T	grains and cereals (1) (T)
June 1971-July 1972	420	7	3	0.1-0.4	fruits (7) (0.1-0.4)
June 1970-April 1971	270	10	7	T-0.25	grains and cereals (1) (T) root vegetables (2) (T) garden fruits (1) (T) fruits (6) (T-0.25)
June 1969-April 1970	360	1	0	0.2	fruits (1) (0.2)

*Sources: Johnson et al., 1981b; Johnson and Manske, 1976, 1977; Manske and Johnson, 1977; Manske and Corneliussen, 1974, 1975; Corneliussen, 1972

T = Trace

2-phenylphenol residue levels found in large fruits for the fiscal years 1970-1976; the following chart includes the data from all years, inclusive, for both domestic and imported large fruits:

Domestic Surveillance

Number of samples	448
None found	347 samples
Trace - 0.03 ppm	26 samples
0.04 - 0.10 ppm	13 samples
0.11 - 0.50 ppm	13 samples
0.51 - 1.00 ppm	15 samples
1.01 - 1.50 ppm	5 samples
1.51 - 2.00 ppm	4 samples
>2.00 ppm	24 samples
Average ppm	0.293

Imported Surveillance

Number of samples	16
None found	15 samples
Trace - 0.03 ppm	1 sample
Average ppm	0.0009

In Japan, Ito et al. (1979) found 2.3 ppm of 2-phenylphenol in whole lemons used for making marmalade. Ishiki et al. (1980) detected no residues of 2-phenylphenol in domestic Japanese citrus fruit samples (detection limit, 1 ppm), but did detect residues in foreign citrus fruits. Chikamoto et al. (1981) analyzed imported fruits and bananas in Kyoto, Japan, for 2-phenylphenol residues; residues (0.1-3.2 ppm) were detected in all citrus fruits, but none was detected in bananas.

Residues of 2-phenylphenol were detected in 86% of samples of varieties of Spanish oranges at levels <10 ppm (Camps Alemany et al., 1980). In Finland, residues of 2-phenylphenol in citrus fruits were detected at levels <10% of maximum levels permissible by FAO/WHO guidelines (Hemminki et al., 1982).

3.3. INHALATION

Monitoring data regarding 2-phenylphenol exposure in the atmosphere were not located in the available literature cited in the Appendices.

3.4. DERMAL

Monitoring data regarding dermal exposure of 2-phenylphenol were not located in the available literature cited in the Appendices.

4. PHARMACOKINETICS

4.1. ABSORPTION

2-Phenylphenol is readily absorbed by the gastrointestinal tract of animals following oral exposure. Nakao et al. (1983) briefly mentioned in a reference to unpublished data from their laboratory that peak plasma levels of radioactivity were reached within 1 hour following oral administration of [^{14}C]-2-phenylphenol to rats. Several investigators have studied the gastrointestinal absorption of 2-phenylphenol in dogs and cats. Peak plasma levels of 2-phenylphenol were reached in 2 hours in adult dogs and puppies, 12 hours in adult cats and 36 hours in kittens following low oral doses (not otherwise specified) of 2-phenylphenol (Rachofsky, 1977). Although specific information concerning rates and amounts of gastrointestinal absorption of 2-phenylphenol were not available, the extent of absorption can be inferred from data regarding excretion (Section 4.4.).

Dermal absorption of 2-phenylphenol in humans has been demonstrated. When a hand disinfectant containing 2% 2-phenylphenol was applied 10 successive times to 11 human volunteers, a mean urinary excretion of 6.2 mg 2-phenylphenol was observed (Harke and Klein, 1981). Infants with varying degrees of dermal exposure to germicidal preparations containing 2-phenylphenol were observed to have detectable amounts of the compound in their serum (Needham et al., 1980). The amounts of 2-phenylphenol found in 0.5-1.0 mL of serum ranged from undetectable to 1.9 µg/mL at an unspecified time after exposure. Of 10 allegedly exposed infants, 7 had amounts of serum 2-phenylphenol >500 ng/mL (Needham et al., 1980).

Information regarding absorption of 2-phenylphenol following inhalation exposure was not located in the available literature. That 2-phenylphenol

can be absorbed by the pulmonary route is inferred from toxicity data: mice exposed continuously to 2-phenylphenol vapors (concentration in air not reported) died within 90 hours (Hanoda, 1977).

4.2. DISTRIBUTION

Information on the distribution of 2-phenylphenol in the tissues of animals is limited. Cats and dogs given radiolabeled (dose, route, vehicle not specified) 2-phenylphenol were observed to have detectable amounts of the compound in several tissues. In decreasing order of concentration, the following were observed to contain 2-phenylphenol: feces, cecum, bile, liver, small intestine, lung, kidney, spleen, muscle, fat, heart, stomach, brain and saliva (Oehme, 1972). It was not reported at what time after administration of the compound the levels were determined.

4.3. METABOLISM

Once ingested, 2-phenylphenol can become conjugated with sulfate and glucuronic acid, possibly in the gastrointestinal tract, where it is made more water soluble (Nakao et al., 1983; Savides and Oehme, 1980). Dawson and Bridges (1979, 1981) demonstrated that incubation of 2-phenylphenol with isolated epithelial cells from guinea pigs resulted in the formation of glucuronide and sulfate conjugates. Oxidation and further conjugation may take place in the liver (Halpaap-Wood et al., 1981a,b; Wiebkin et al., 1978). Approximately 99% of the urinary metabolites of 2-phenylphenol in male and female F344 DuCrj rats that had received diets containing 20,000 ppm 2-phenylphenol sodium salt for 136 days were glucuronic acid conjugates of 2-phenylphenol and 2,5-dihydroxybiphenyl (the 2,5-diol), with traces of 2,5-diquinone biphenyl (Nakao et al., 1983). Savides and Oehme (1980) treated puppies, dogs, kittens and cats with 3.7 [^{14}C]-2-phenylphenol (uniformly labeled) (average doses were 2.03, 0.27, 2.04 and 1.16 mg/kg,

respectively) on 25 alternate days. Free 2-phenylphenol accounted for 73-98% of urinary radioactivity. The glucuronic acid and the sulfate conjugates amounted to mean percentages ranging from 0.76-21.1% and 2.4-8.3%, respectively, of the urinary radioactivity among the groups.

Evidence for further conjugation and oxidation by the liver has been obtained from *in vitro* and *in vivo* studies. Wiebkin et al. (1978) incubated 2-phenylphenol with isolated rat intact hepatocytes. Sulfate and glucuronic acid conjugates were formed. At low concentrations of 2-phenylphenol, the sulfate conjugation exceeded glucuronic acid conjugation; however, as the concentration of 2-phenylphenol increased and the sulfate conjugation process became saturated, the glucuronic acid conjugates predominated. Halpaap-Wood et al. (1981a,b) studied the *in vivo* and *in vitro* metabolism of 2-phenylphenol in rats and mice. Noninduced male Sprague-Dawley rats and β-naphthoflavone-induced male C57Bl mice were treated intraperitoneally with 2-phenylphenol at 30 and 60 mg/kg, respectively. In the rat, the urinary metabolites were 2,5- and 2,4-diols excreted in a 2:1 ratio. In the induced mice, the 2,5- and 2,3-diols were excreted in a 6:1 ratio. When 2-phenylphenol was incubated with microsomal enzymes prepared from noninduced or 3-methylcholanthrene-induced Spague-Dawley rats and Ha/ICR mice, only the 2,3- and 2,5-diols were formed. During incubation of purified rat liver microsomes with 1.1×10^{-4} and 1.1×10^{-3} M [^{14}C]-2-phenylphenol, 33.8 and 55.8%, respectively, of the radioactivity was present as diols (Reitz et al., 1983).

Reitz et al. (1983) investigated the mechanisms of 2-phenylphenol toxicity in the rat and postulated mechanistic pathways for its metabolism (Figure 4-1). A strong dose-dependent response of 2-phenylphenol metabolism in rats was observed. The urinary metabolites from rats given single gavage

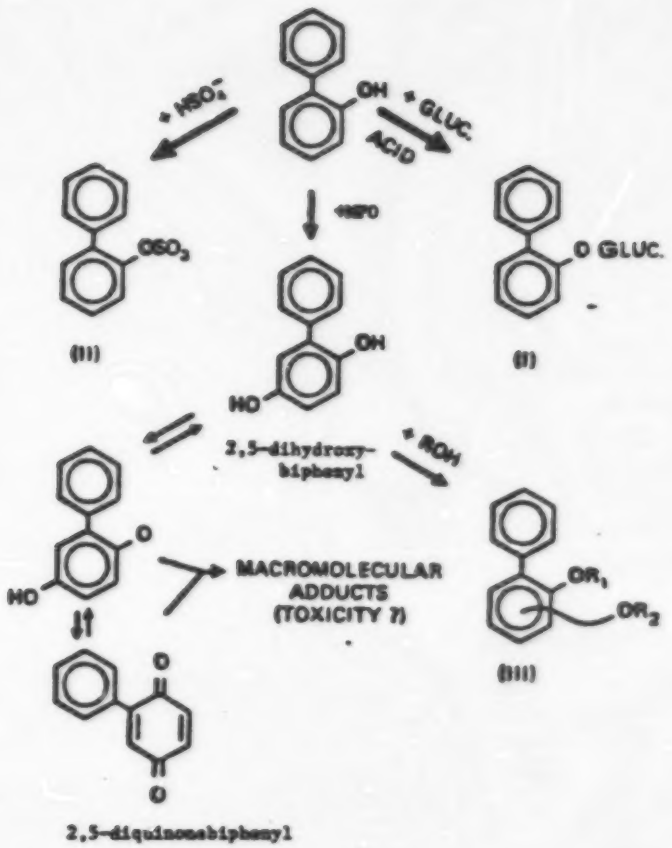


FIGURE 4-1

Hypothetical Pathways for the Metabolism of 2-Phenylphenol in the Rat

Source: Reitz et al., 1983

doses of 5, 50 or 500 mg/kg of [^{14}C]-2-phenylphenol (uniformly labeled in the phenyl ring) or its sodium salt were evaluated by HPLC and direct probe electron impact mass spectroscopy. No apparent differences in the chromatograms of urine from rats treated with either compound were observed. In the animals given 5 or 50 mg/kg, the amount of free 2-phenylphenol and the free 2,5-diol in the urine 24 hours after administration accounted for <2% of the total urinary radioactivity. Most of the urinary radioactivity in these animals was in the form of sulfate ester (see I in Figure 4-1) and glucuronic acid conjugates (see II in Figure 4-1) of 2-phenylphenol. A third metabolite (see III in Figure 4-1) was observed in the urine of rats given 500 mg/kg that was not present at lower doses. This third metabolite was tentatively identified as a sulfate and/or glucuronide conjugate of dihydroxybiphenyl. Approximately 25% of the urinary radioactivity excreted by rats given 500 mg/kg 2-phenylphenol was contained in the chromatographic fraction corresponding to Metabolite III. The investigators hypothesized that diols formed by mixed function oxidases can form additional products that can bind to biomacromolecules. As mentioned previously, Nakao et al. (1983) detected traces of 2,5-diquinonebiphenyl in rat urine following administration of 2-phenylphenol sodium salt.

4.4. EXCRETION

2-Phenylphenol and its metabolites are excreted primarily via urine in mammals. Reitz et al. (1983) gave groups of four fasted male F344 rats a single gavage dose of 500 mg 2-phenylphenol or its sodium salt to which 7-8 µCi of the respective uniformly [^{14}C]-labeled compound was added. Urinary excretion within 24 hours accounted for ~96 and 91% of the administered radioactivity in the 2-phenylphenol and 2-phenylphenol sodium salt doses, respectively. Fecal excretion within 24 hours accounted for ~6% of the administered radioactivity for either compound.

Nakao et al. (1983) measured the amount of 2-phenylphenol excreted daily as a conjugate or free compound in rats fed diets containing 2% of the sodium salt 5 days/week for 136 days. The daily intakes of 2-phenylphenol were estimated to be 247.9 and 159.4 mg for males and females, respectively. The percentage of the daily dose excreted in the urine was ~55 and 39% in the males and females, respectively.

Puppies and dogs excreted ~45 and 54%, respectively, of the administered radioactivity from ^{14}C-2-phenylphenol as parent compound and conjugates within weeks (Savides and Oehme, 1980). Similarly, kittens and cats excreted ~31 and 42% of the dose after 3 and 6 weeks, respectively. The animals had received ~3.7 mg of the compound every other day for 50 days (25 doses).

5. EFFECTS

5.1. CARCINOGENICITY

Hiraga and Fujii (1981) studied the carcinogenicity of 2-phenylphenol sodium salt (technical grade Dowicide A, ≥95% pure) fed to rats for durations of 13 or 91 weeks. In the 91 week study groups of 20 or 21, 5-week-old male F344 DuCrj rats were maintained on diets containing 0, 1250, 2500, 5000, 10,000, 20,000 or 40,000 ppm 2-phenylphenol sodium salt. The mean intakes of OPP-Na, as reported by the investigators were 62, 125, 250, 500, 1000 and 2000 mg/kg bw/day, respectively. Survival was 90, 90, 95, 90, 90, 57 and 71%, respectively. Routine pathological evaluation (gross and microscopic examination of major tissues and organs and gross lesions) was performed on all rats that died spontaneously, were killed in extremis or were sacrificed at the end of the study. A variety of urinary tumors in treated rats was observed. The incidence of transitional cell carcinomas in the renal papilla, renal pelvis and urinary bladder in treated rats and control rats are presented in Table 5-1. Other toxic effects in the kidneys were observed and are discussed in Section 5.5.

Hiraga and Fujii (1981) observed a low incidence of urinary bladder tumors in the subchronic (13-week) portion of their study. Groups of 9 or 10 male and 9 or 10 female 4-week-old F344 DuCrj rats were maintained for 13 weeks on diets containing 0, 1250, 2500, 5000, 10,000, 20,000 or 40,000 ppm 2-phenylphenol sodium salt. As estimated by the investigators, these diets provided 0, 85, 177, 353, 706, 1384 and 2487 mg 2-phenylphenol sodium salt/kg/day, respectively, for the males, and 87, 177, 352, 706, 1338 and 2431 mg 2-phenylphenol sodium salt/kg/day, respectively, for the females. All rats survived the 13 weeks of treatment, at which time they were sacrificed. Upon routine gross and microscopic histologic evaluation, urinary bladder tumors, classified as papillomas and transitional cell carcinomas,

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TABLE 5-1

Incidence of Transitional Cell Carcinoma in the Urinary Bladder, Renal Papilla and Renal Pelvis of Male Rats Treated with 2-Phenylphenol Sodium Salt in the Diet for 91 weeks[a]

Target Organ	Dietary Concentration (ppm)						
	0	1250	2500	5000	10,000	20,000	40,000
Urinary bladder	0/20	0/20	0/20	0/21	6/21	19/21[b]	8/20
Renal papilla	0/20	0/20	0/20	1/21	0/21	1/21	10/20
Renal pelvis	0/20	0/20	0/20	1/21	1/21	0/21	3/20
Total incidence (no. of tumor-bearing rats)	0/20	0/20	0/20	1/21	7/21	20/21	17/20

[a]Source: Hiraga and Fujii, 1981

[b]One of the tumors in this group was a carcinosarcoma with epithelial and connective tissue differentiation.

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were observed. The incidences in male rats are presented in Table 5-2. No carcinomas were observed in females; however, 2/10 female rats at the highest level had papillomas. No papillomas were found in other female groups.

It was mentioned in a report of a study on the in vivo metabolism of 2-phenylphenol sodium salt that ~70% of the male F344 DuCrj rats developed bladder tumors after 136 days of dietary exposure to 20,000 ppm (Nakao et al., 1983). Controls and female rats did not have bladder tumors. There were five rats/sex/group. The results are uncertain since a 70% tumor incidence was reported for a group of five males.

Reitz et al. (1983) of Dow Chemical Company failed to find urinary bladder tumors in groups of 30 male F344 rats maintained on diets containing 2-phenylphenol or 2-phenylphenol sodium salt at 20,000 ppm for up to 90 days [compare with Hiraga and Fujii (1981) (13-week study)]. Other organs examined histologically (kidney, liver, stomach, prostate and urethra) were also free of tumors. This study is discussed more fully in Section 5.5.

In a 2-year study designed to assess the toxicologic effects of 2-phenylphenol, Hodge et al. (1952) maintained groups of 25 male and 25 female Wistar rats on diets containing 2-phenylphenol at 0, 200, 2000 or 20,000 ppm. Survival was not reported. Gross and histological examination of rats killed at the end of the experiment revealed no evidence of a carcinogenic effect on heart, lung, spleen, stomach, large intestine, liver, adrenal, urinary bladder, testes, brain or bone marrow. Further information regarding toxic effects observed in this study is presented in Section 5.5.

Two hybrid strains of mice, (C57BL/6 x C3H/Anf)F_1 = B6C3F_1 and (C57BL/6 x AKR)F_1 = B6AKF_1, were treated with 100 mg 2-phenylphenol/kg (the MTD), which was determined from the average body weight of mice and not corrected for weight gain) in 0.5% gelatine daily by gavage from days 7-28 of age, after which 2-phenylphenol was given in the diet at a concentration

TABLE 5-2

Incidence of Urinary Bladder Tumors in Male Rats Treated with 2-Phenylphenol in the Diet for 13 Weeks*

Tumor Type	Dietary Concentration (ppm)						
	0	1250	2500	5000	10,000	20,000	40,000
Papillomas	0/10	0/10	0/10	0/9	1/10	4/10	0/10
Transitional cell carcinoma	0/10	0/10	0/10	0/9	0/10	5/10	1/10
Total (no. of rats with tumors)	0/10	0/10	0/10	0/9	1/10	9/10	1/10

*Source: Hiraga and Fujii, 1981

of 280 ppm for up to ~18 months (BRL, 1968; Innes et al., 1969). Negative controls consisted of 72 untreated mice/sex/strain and 18 vehicle-treated mice/sex/strain. The treated group consisted of 18 male and 18 female mice of each strain. Survival and growth rates were comparable among the groups. At the end of the treatment, the mice were sacrificed and necropsied. There were no significant increased incidences of tumors compared with controls.

$B6C3F_1$ and $B6AKF_1$ mice (18 mice/sex/strain) were given one-time subcutaneous injections of 1000 mg 2-phenylphenol/kg in corn oil at 28 days of age and killed after 18 months (BRL, 1968). The control groups consisted of 24 corn oil treated mice/sex/strain and >100 untreated mice/sex/strain. There were no significant increased incidences of tumors compared with controls.

Ito et al. (1983) reported that following initiation of F344 rats with 100 ppm N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) in the drinking water for 4 weeks, 2-phenylphenol at 20,000 ppm in the drinking water for 36 weeks did not promote urinary bladder cancer.

A carcinogenicity bioassay of 2-phenylphenol is being prepared by NTP (1984). The study protocol involved a long-term skin painting experiment of 2-phenylphenol in mice (Powers, 1981). The drafting of the technical report is currently in progress (NTP, 1984).

5.2. MUTAGENICITY

The results of mutagenicity testing of 2-phenylphenol are summarized in Table 5-3. Negative results have been obtained in most assays for reverse mutation in eight strains of Salmonella typhimurium and two strains of Escherichia coli with or without metabolic activation by rat liver S-9 enzymes (Shirasu et al., 1978; Moriya et al., 1983; Reitz et al., 1983; Hirayama et al., 1981; Probst et al., 1981; McMahon et al., 1979) and in S. typhimurium strain G46 in the mouse host-mediated assay (Shirasu et al.,

TABLE 5-3

Mutagenicity Data for 2-Phenylphenol

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Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537 and TA1538	NR	NR	±	-	NC	Shirasu et al., 1978*
Reverse mutation host mediated	S. typhimurium G-46	oral	200 or 600 mg/kg/day for 5 days	JCL-ICR male mice	-	NC	Shirasu et al., 1978*
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	NR	±	+	weak dose-response mutagenicity for TA98, negative for TA100	Nishioka and Ogasawara, 1978*
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	plate incorporation	<5 mg/plate	+ rat liver S-9	-	NC	Moriya et al., 1983
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	pre-incubation plate incorporation	0.25-250 µg/plate	+ rat liver S-9	-	toxic >250 µg/ml -S9	Reitz et al., 1983
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	1-100 µg/plate	+ rat liver S-9	-	toxic at 100 µg/plate on TA 100 (+S9)	Hirayama et al., 1981
Reverse mutation	S. typhimurium G46, TA1535, TA100, C3076, TA1537, D3052, TA1538, TA98	gradient test	0.1-1000 µg/plate (calculated)	+ rat liver S-9	-	NC	Probst et al., 1981; McMahon et al., 1979
Reverse mutation	Escherichia coli WP2, WP2 urvA-	plate incorporation	0.1-1000 µg/plate	+ rat liver S-9	-	NC	Probst et al., 1981; McMahon et al., 1979
Reverse mutation	E. coli, WP2 hcr	plate incorporation	<5 mg/plate	+ rat liver S-9	-	NC	Moriya et al., 1983
Reverse mutation	E. coli, WP2 hcr	NR	NR	+ rat liver S-9	-	NC	Shirasu et al., 1978*

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TABLE 5-3 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Rec assay	Bacillus subtilis H17 and M45	NR	NR	NR	-	NC	Shirasu et al., 1978*
DNA repair	E. coli, WP2 WP2 uvrA, CM571 and WP100	paper disc	1-4 mg/disc	none	+	NC	Hirayama et al., 1981
DNA repair	E. coli, WP2 WP2 uvrA, CM571 and WP100	NR	NR	none	+	NC	Nishioka and Ogasawara, 1978*
Unscheduled DNA synthesis	F344 rat hepatocytes	liquid holding	<100 nmoles/ml	NA	-	NC	Probst et al., 1981
Unscheduled DNA synthesis	F344 rat hepatocytes	cell culture	10^{-3} to 10^{-2} M (employed Na salt)	NA	-	toxic to cells at 10^{-2} and 10^{-3}	Reitz et al., 1983
Chromosome abnormalities	guinea pig ovarian cells	NR	NR	none	-	NC	Yoshida et al., 1978*
Chromosome aberrations	human diploid fibroblasts	NR	0.2-1.0 µg/ml for 24 hours	none	+	Positive dose-response	Takahashi, 1978*
SCE	Chinese hamster ovary KI cells	liquid holding	5-50 µg/ml	none	-	cell growth inhibited at 50 µg/ml	Nawai et al., 1979*
Chromosome abnormalities	male Wistar rats	oral	50-800 mg/kg/day for 5 days	NA	-	NC	Shirasu et al., 1978*
Chromosome abnormalities	male Wistar rats	oral	250-4000 mg/kg single dose	NA	-	NC	Shirasu et al., 1978*
Chromosome aberrations	rats, bone marrow	oral	312.5-1250 mg 2-phenylphenol/kg/ day for 13 weeks	NA	-	NC	Yoshida and Hiraga, 1982*
Chromosome aberrations	rats, bone marrow	oral	276.7-553.4 mg 2-phenylphenol/kg/ day for 104 weeks (employed Na salt)	NA	-	NC	Yoshida and Hiraga, 1982*
Dominant lethal	C3H male mice	oral	100, 500 mg/kg/day for 5 days	NA	-	NC	Kaneoa et al., 1979; Shirasu et al., 1978*

* = Abstract; NA = Not applicable; NC = No comment; NR = Not reported

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1978); in the rec assay using Bacillus subtilis strains H17 and M45 (Shirasu et al., 1978); for unscheduled DNA synthesis in rat hepatocytes whether tested as 2-phenylphenol (Probst et al., 1981) or as the sodium salt (Reitz et al., 1983); for chromosome aberrations in guinea pig ovary cells (Takahashi, 1978) or in rat bone marrow cells when the 2-phenylphenol sodium salt (Yoshida and Hiraga, 1982) or 2-phenylphenol were tested (Shirasu et al., 1978; Yoshida and Hiraga, 1982); for SCE in Chinese Hamster ovary cells (Nawai et al., 1979) and in the dominant lethal assay in mice (Shirasu et al., 1978). In addition to the negative results summarized in Table 5-3, Reitz et al. (1983) reported that [^{14}C]-2-phenylphenol or [^{14}C]-2-phenylphenol sodium salt was not bound to DNA isolated from the urinary bladder of rats following treatment by gavage with the radiolabeled compounds at 500 mg/kg. The majority of studies have been reported in abstract form and therefore allow limited evaluation.

Positive results for mutagenicity were indicated in a study reported in abstract form. Nishioka and Ogasawara (1978) found a weakly positive dose-response for reverse mutation in S. typhimurium TA98 (but not TA100) with and without metabolic activation; however, concentrations of 2-phenylphenol tested were not reported. The overwhelming evidence from Table 5-3 indicates that 2-phenylphenol does not produce reverse mutations in bacteria at concentrations $\leq$5 mg/plate. When 2-phenylphenol was tested for DNA repair in E. coli, Hirayama et al. (1981) reported negative results, while Nishioka and Ogasawara (1978) reported positive results using the same strains (see Table 5-3). In an abstract of a Japanese study, it was reported that a mixture of 30 µg 2-phenylphenol and 1000 µg thiabendazole/plate resulted in a 3-fold increase in revertant colonies (Fujita and Hiraga, 1980). The bacterial strain and the response of thiabendazole alone were not reported; however, the investigators stated that 2-phenylphenol was a weak co-mutagen.

5.3. TERATOGENICITY

Teratogenic effects of 2-phenylphenol administration to laboratory animals have not been demonstrated.

John et al. (1981) of Dow Chemical Company treated groups of 25-27 pregnant Spague-Dawley rats by gavage with 2-phenylphenol (99.69% pure) in cottonseed oil at doses of 100, 300 or 700 mg/kg day on days 6-15 of gestation. The control group consisted of 35 pregnant vehicle-treated rats. Day 0 of gestation was defined as the day on which vaginal smears were sperm positive. The dams were sacrificed on day 21 of gestation. There were no deaths attributable to treatment; one dam at 700 mg/kg died as a result of a laboratory accident. The mean body weight gain of the 700 mg/kg dams was significantly ($p<0.05$) reduced to 36% of control only during days 6-9 of gestation. Body weight gains were slightly reduced in this group and the lower dose groups throughout the study compared with controls, but the differences were not statistically significant. The absolute liver weights were lower than control for all treated groups, although only the reduction in the 700 mg/kg group (92% of control) was statistically significant ($p<0.05$). No significant differences among groups were observed for percentage of pregnancies, implantation sites/dam, live fetuses/litter, resorptions/litter, sex ratio, mean fetal body weight and mean fetal crown-rump length. One dam at 300 mg/kg resorbed all fetuses. Fetuses were examined for external abnormalities, soft tissue anomalies and skeletal defects. At 300 mg/kg, one fetus had a hypoplastic tail and was missing a sacral vertebra and all caudal vertebrae. No major malformations were observed in other groups. Statistically significant increased incidences of skeletal variations were observed only in the 700 mg/kg group of fetuses. The incidence (number of fetuses affected/number of litters affected) of delayed

ossification of sternebrae was 10/6 in the 700 mg/kg group compared with 5/5 in controls ($p<0.05$). The incidence of foramina in the skull was 6/6 in the 700 mg/kg group and 5/5 in controls ($p<0.05$).

Kaneda et al. (1978) gave pregnant rats oral doses of 150-1200 mg 2-phenylphenol/kg/day from days 6-15 of gestation. Maternal and fetal toxicity (death) were observed at >300 mg/kg/day, but no significant increases in terata were observed. Further details were not provided in the abstract. Ogata et al. (1978) gave pregnant mice oral doses of 1450, 1740 or 2100 mg 2-phenylphenol/kg/day or 100, 200 or 400 mg 2-phenylphenol sodium salt/kg/day on days 7-15 of gestation. Maternal and fetal toxicity were observed (i.e., reduced body weight gain and organ weight changes), but no teratological effects were observed. Further details were not provided in the abstract.

5.4. OTHER REPRODUCTIVE EFFECTS

Increased testicular weight was observed in male Wistar rats maintained for 2 years on a diet containing 20,000 ppm 2-phenylphenol (Hodge et al., 1952) (Section 5.5.).

Pertinent data regarding other adverse effects of 2-phenylphenol on reproduction were not located in the available literature cited in the Appendices.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Hodge et al. (1952) maintained groups of 25 male and 25 female weanling Wistar rats for 2 years on diets containing 0, 200, 2000 or 20,000 ppm of 2-phenylphenol (>98% purity). The investigators reported that no treatment-related effect on mortality was observed; however, data were not provided and food consumption was not recorded. Average weekly body weights in the groups receiving 0-2000 ppm were not significantly different; however, significant reduction was observed in the 20,000 ppm treatment group. At

the end of 1 year, the mean body weights were 90% (p=0.001) and 94% (p=0.01) of control for the males and females, respectively. Urine and blood samples were collected at intervals throughout the experiment. 2-Phenylphenol-treated groups were not different from controls regarding urinary sugar and protein or hematological indices. Surviving animals were killed at the end of the study and examined for gross and histopathological lesions. No effects of treatment were observed on organ weights, with the exception of testicular weights. Mean relative testes weights were 6.5, 8.1, 7.6 and 9.5 g/kg bw for the 0, 200, 2000 and 20,000 ppm groups, respectively. No effects of treatment were observed in the pathology of heart, lung, spleen, stomach, large intestine, liver, adrenal, bladder, testes, brain or bone marrow tissues. Renal damage was observed (tubular dilation and inflammation) in rats at the 20,000 ppm level, but not in other groups. Detectable amounts ($\geq$1 µg/sample) of 2-phenylphenol were found in the kidneys of rats at 2000 ppm (1 mg/100 g tissue) and at 20,000 ppm (22 mg/100 g), but not in other tissues at any treatment level.

Hiraga and Fujii (1981) maintained groups of ~20 male F344/DuCrj rats on diets containing 2-phenylphenol sodium salt at 0, 1250, 2500, 5000, 10,000, 20,000 or 40,000 ppm for 91 weeks. In addition to the tumors of the urinary tract (see Section 5.1.), non-neoplastic renal toxicity was observed. Renal toxicity consisted of severe pyelonephritis with papillary destruction, and/or marked cystic dilation of the tubles occurred in 19/20 rats at 40,000 ppm and 1/21 rats at 20,000 ppm. The investigators stated that the severity and incidence of pyelonephritis was markedly greater in the 40,000 ppm group than in other groups; however, the incidence and severity in other groups was not reported. Pyelonephritis was also observed in rats treated at 40,000 ppm for 13 weeks: the lesion was moderate in 6/10 males and slight in

1/10 females. Treated rats, but not control rats, had inconsistent instances of hematuria beginning at 45 weeks of treatment.

Nakamura et al. (1982) maintained male rats (number and strain not specified) on diets containing 0, 6250, 12,500 or 25,000 ppm 2-phenylphenol for 91 weeks. Body weights, food and water consumption, tissue weights, survival, urine chemistry and blood chemistry were determined to assess the toxicity of the compound. Body weights and growth rates were observed to decrease in a dose-related manner. Food consumption was significantly decreased in the 25,000 ppm group. Water consumption was increased in a dose-related manner. Survival rates were 90, 65 and 60% in the 6250, 12,500 and 25,000 ppm groups, respectively. Cholesterol content of the blood was significantly decreased in the 625 and 1250 mg/kg/day groups. Kidney, testes and gall bladder tissue weights were slightly increased, and the spleen-to-body weight ratios were observed to decrease. Urinary protein was significantly decreased and hematuria and urinary calculi were observed in some animals. There was a tendency for increased BUN and white blood cell counts. Further detail was not provided in the abstract.

In a 6-month study, groups of five male and five female albino rats were treated by gavage with 2-phenylphenol (≥98% pure) at doses of 0, 50, 100, 200 and 500 mg/kg/day 5 days/week (Hodge et al., 1952). There were no effects of treatment on growth rate or mortality. Mean weights of livers and kidneys were slightly increased in the 500 mg/kg group. Results of hematologic evaluation of 100 and 500 mg/kg groups were within normal limits; other groups were not tested. There were no treament-related histopathological lesions in the rats sacrificed at the end of the study. Further details were not provided in the brief report.

Hodge et al. (1952) treated groups of 12 male and 12 female rats (strain not specified) at dietary levels of 0, 1000, 3000, 10,000 and 20,000 ppm 2-phenylphenol (≥98% pure) for 3 months. The 20,000 ppm rats had slightly reduced mean body weight gain. There was no effect on mortality in any group. Hematologic BUN values were within normal limits for the 20,000 ppm group; the other groups were not tested. At the end of the study, the rats were killed and examined for gross and histopathologic lesions. The livers, kidneys and spleens of some of the 10,000 and 20,000 ppm rats were reported to be slightly increased; however, specific data were not provided. No treatment-related lesions were observed in lungs, heart, kidney, spleen, adrenal, pancreas, testes, stomach and bladder.

Reitz et al. (1983) of Dow Chemical Company maintained groups of 30 male F344 rats for 90 days on control diets or diets containing 20,000 ppm 2-phenylphenol or 20,000 ppm 2-phenylphenol sodium salt. 2-Phenylphenol was 99.8% pure and the sodium salt contained 72.0% 2-phenylphenol sodium salt, 25.6% water and 1.05% NaOH. It was stated that on a molar basis, 20,000 ppm of 2-phenylphenol by weight was equivalent to 31,000 ppm 2-phenylphenol sodium salt by weight. Mean food consumption was reduced to ~14 and 80% of control for the 2-phenylphenol and the 2-phenylphenol sodium salt groups, respectively, during the first week. Food consumption was restored to near control level (although it remained somewhat reduced) thereafter. Mean body weight was likewise reduced to ~65 and 90% of control in the 2-phenylphenol and the 2-phenylphenol sodium salt groups, respectively, after the first week. Thereafter, the animals gained weight at a rate comparable to controls; however, body weights remained reduced. After 83 days on diet, the mean body weight of the 2-phenylphenol group was ~80% of control, and the mean body weight of the rats receiving the sodium salt was ~90% of control.

BUN and serum creatinine content were normal throughout the study, with the exception of a 30% increased BUN at 1 week (coincident with malnutrition) in the 2-phenylphenol group. Urinalysis values were normal throughout the study with the exception of a significant (no p value reported) decrease in urine specific gravity at 65 and 90 days in 2-phenylphenol group. Histological evaluation was performed on random samples of 3-7 rats/group after 3, 7, 14, 30, 65 and 90 days of treatment. Hyperplasia and inflammatory cell infiltration of the bladder epithelium were observed in the 2-phenylphenol sodium salt exposed group, but not in controls or 2-phenylphenol exposed animals. Rats receiving 2-phenylphenol had focal cortical cysts, multiple areas of focal tubular collapse, atrophy in the kidney cortex and cystic degeneration of the kidneys. Slightly swollen cells were observed in the livers of treated rats of both groups. No other signs of toxicity were observed in the liver.

Kobayashi et al. (1982) maintained male and female rats (strain and number not specified) on diets containing 20,000 2-phenylphenol sodium salt for 159 days. The effects of treatment were determined on urine alkaline phosphatase activity and blood biochemical indices. Alkaline phosphatase activity was reduced 24 hours after the start of treatment and remained low throughout the experiment. Glutamic oxalacetic transaminase activity was observed to decline in female rats. Further experimental details were not available from the abstract.

Hodge et al. (1952) maintained groups of two mongrel dogs for 1 year on diets providing 0, 20, 200 and 500 mg 2-phenylphenol/kg/day. No effects of treatment were observed on hematological parameters, urine sugar and protein or tissue pathology (heart, lung, spleen, stomach, large intestine, liver, adrenal, bladder, testes, brain, bone marrow, pancreas, uterus, ovary and

thyroid) at any dose level. No effects were observed on organ weights except for an increase in kidney-to-body weight ratio in the 500 mg/kg/day dogs (6.3 g/kg bw compared with 3.3-5.3 g/kg bw in all other groups).

5.6. OTHER RELEVANT INFORMATION

2-Phenylphenol has a low order of acute toxicity, as evidenced by the LD_{50} of a rat and mouse population (Table 5-4).

Data are available regarding the potential effects of 2-phenylphenol on the immune system. Administration of the compound has been observed to result in significant concentrations in the spleens of dogs and cats (LaVia et al., 1979). Administration of 0.7 mg 2-phenylphenol/kg/day in the drinking water for 3 weeks to mice resulted in significant immunodepression in spleen cells. A significant reduction in numbers of splenic macrophages were observed in mice given 0.5 mg 2-phenylphenol/kg/day (LaVia et al., 1979). Conversely, Luster et al. (1981) reported no effect of 2-phenylphenol exposure (200 mg/kg/day x 10 days by gavage) to mice was observed on immune functions or host susceptibility.

TABLE 5-4

Acute Lethal Doses of 2-Phenylphenol*

Species	Route	LD_{50} (mg/kg)
Rat	oral	2000-2700
Mouse	oral	900
Mouse	intraperitoneal	50

*Source: NIOSH, 1977

6. AQUATIC TOXICITY

Data on the toxicity of 2-phenylphenol to aquatic organisms are limited to that reported by Applegate et al. (1957). A concentration of 5.0 mg/ℓ in static, aerated conditions had no lethal effects in larval lamprey, Petromyzon marinus, exposed for 24 hours. Additional data regarding the acute or chronic toxicity or effects on aquatic plants were not located in the available literature. Connell and Miller (1981) reported that a level of 1.0 mg/ℓ could cause the organoleptic detection of 2-phenylphenol in tissues of exposed aquatic organisms. Pertinent data regarding other aspects of the aquatic toxicity of 2-phenylphenol were not located in the available literature cited in the Appendices.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The U.S. EPA has established tolerances of 5-25 ppm for 2-phenylphenol or its sodium salt in or on a variety of agricultural commodities (Federal Register, 1981). When added to rubber or polymers that contact food, the level of 2-phenylphenol in that rubber or polymer may not exceed 5% (w/w) (Federal Register, 1981).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 2-phenylphenol were not located in the available literature.

8. RISK ASSESSMENT

The chronic administration of 2-phenylphenol has been observed to cause adverse effects on the kidneys of Wistar and F344 rats (Hodge et al., 1952; Nakamura et al., 1982; Hiraga and Fujii, 1981). In subchronic feeding studies, Reitz et al. (1983) observed that 2-phenylphenol caused severe renal effects in F344 rats. Similar administration of the sodium salt at lower dietary levels (on a molar basis) resulted in no adverse renal effects; rather, adverse changes in bladder epithelial morphology were observed.

Carcinogenicity data from dietary studies are equivocal. Hiraga and Fujii (1981) reported the induction of tumors (transitional cell carcinomas of the urinary bladder) in F344 rats by the chronic or subchronic dietary administration of 2-phenylphenol sodium salt. F344 rats receiving diets containing 20,000 ppm 2-phenylphenol sodium salt for 136 days also developed bladder tumors (Nakao et al., 1983), although insufficient detail was included to evaluate this study; however, administration of 2-phenylphenol to Wistar rats for 2 years (Hodge et al., 1952) or mice for ~18 months (Innes et al., 1969; BRL, 1968) did not result in tumor formation. IARC (1983) concluded that, while the available data are inadequate for the evaluation of the carcinogenicity of 2-phenylphenol to experimental animals, studies in rats provide limited evidence of the carcinogenicity of 2-phenylphenol sodium salt to experimental animals.

Until additional carcinogenicity data are available, the tumor incidence data of Hiraga and Fujii (1981) may be used to calculate a q_1^* for humans.

The use of data regarding the carcinogenicity of 2-phenylphenol sodium salt in quantitative risk assessment for 2-phenylphenol may be justified for the following reasons. The sodium salt will be converted to 2-phenylphenol in the acid environment of the stomach. Although data quantitating the rate and extent of absorption of these compounds from the gastrointestinal tract are not available, urinary excretion data do not indicate substantial differences in absorption between the two compounds. Regardless of whether radiolabeled 2-phenylphenol or its sodium salt was administered, >90% of the administered radioactivity was excreted in the urine within the first 24 hours after rats were gavaged with 500 mg/kg of compound (Reitz et al., 1983b).

In the carcinogenicity study by Hiraga and Fujii (1981), the incidence of transitional cell carcinoma in male rats was 0/20, 0/20, 0/20, 0/21, 6/21, 19/21 and 8/20 for groups receiving dietary levels of 0, 1250, 2500, 5000, 10,000, 20,000 and 40,000 ppm 2-phenylphenol sodium salt for 637 days, respectively. As estimated by the investigators, these dietary levels provided doses of 0, 62, 125, 250, 500, 1000 or 2000 mg 2-phenylphenol sodium salt/kg/day. The doses are calculated to be equivalent to 0, 54.9, 110.7, 221.3, 442.8, 885.5 and 1771.1 mg 2-phenylphenol/kg/day (obtained by multiplying by the molecular weight ratio of free compound/salt). Using these data and the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980b), a q_1^* of 1.94×10^{-3} $(mg/kg/day)^{-1}$ can be derived for humans. The conversion factor used in the calculation of this q_1^* for humans (assuming 70 kg body weight) from animal data was the cube root of the body weight ratio (Federal Register, 1980), which has been demonstrated empirically to adjust for species to species extrapolation.

EPA's Office of Pesticide Programs (OPP), however, has computed the equivalent animal doses to be 0, 39, 78, 155, 312.5 and 625 mg 2-phenylphenol/kg/day for the 0, 1250, 2500, 5000, 10,000 and 20,000 ppm dietary levels, respectively. (No mg/kg equivalent dose was calculated for the 40,000 ppm level, due to problems with the goodness-of-fit at this dosage.) Using the same tumor incidence data, a q_1^* of 1.57×10^{-3} $(mg/kg/day)^{-1}$ was determined. An assumed human body weight of 60 kg also contributes somewhat to the difference between these two q_1^* values. This latter value is the q_1^* currently published by the U.S. EPA.

Complete data for the derivation of the q_1^*s are presented in Appendices B and C.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data, but no studies of carcinogenicity or chronic toxicity were available. A 30-day study in rats, comparing the effects of equimolar dietary levels of 2-phenylphenol and its sodium salt, demonstrated that although both compounds were toxic to the bladder and kidney, 2-phenylphenol sodium salt was more toxic than was 2-phenylphenol. Sodium did not contribute to the toxicity. Data regarding the dose-dependence of macromolecular binding *in vivo* were presented as evidence that when 2-phenylphenol is administered orally to rats as the sodium salt rather than as free compound, it is more available to saturate detoxication processes in the bladder, kidney and liver.

It was suggested that the greater availability was due to greater absorption, but no direct evidence of greater absorption was presented. These data provide evidence that differences in the biological activities of 2-phenylphenol and 2-phenylphenol sodium salt are quantitative rather than qualitative and support the concern that 2-phenylphenol, as well as the sodium salt, may be carcinogenic.

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APPENDIX A

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in July and August, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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APPENDIX B

CANCER DATA SHEET FOR DERIVATION OF q_1^*

(based upon equivalent dosage information provided in the study)

Compound: 2-Phenylphenol (sodium salt)
Reference: Hiraga and Fujii, 1981
Species, strain, sex: Rats, F344, male
Body weight: 0.35 kg (assumed)
Length of exposure (le) = 637 days
Length of experiment (Le) = 637 days
Lifespan of animal (L) = 730 days
Tumor site and type: Transitional cell carcinoma, urinary bladder
Route, vehicle: oral, diet

Experimental Doses or Exposures		INPUT	
		Transformed Dose 2-Phenylphenol (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
2-Phenylphenol Sodium Salt	2-Phenylphenol (mg/kg/day)		
0 ppm = 0 mg/kg/day	0	0	0/20
1250 ppm = 62 mg/kg/day	54.9	54.9	0/20
2500 ppm = 125 mg/kg/day	110.7	110.7	0/20
5000 ppm = 250 mg/kg/day	221.3	221.3	0/21
10,000 ppm = 500 mg/kg/day	442.8	442.8	6/21
20,000 ppm = 1000 mg/kg/day	885.5	885.5	19/21
40,000 ppm = 2000 mg/kg/day	1771.1	1771.1	8/20

Unadjusted q_1^* from study = 2.2108×10^{-4} $(mg/kg/day)^{-1}$

Human q_1^* = 1.94×10^{-3} $(mg/kg/day)^{-1}$

APPENDIX C

CANCER DATA SHEET FOR DERIVATION OF q_1^*

(as calculated by OPP)

Compound: 2-Phenylphenol (sodium salt)
Reference: Hiraga and Fujii, 1981
Species, strain, sex: Rats, F344, male
Body weight: 0.35 kg (assumed)
Length of exposure (le) = 637 days
Length of experiment (Le) = 637 days
Lifespan of animal (L) = 730 days
Tumor site and type: Transitional cell carcinoma, urinary bladder
Route, vehicle: oral, diet

Experimental Doses or Exposures		Incidence
2-Phenylphenol Sodium Salt	2-Phenylphenol (mg/kg/day)	No. Responding/No. Tested (or Examined)
0 ppm	0	0/20
1250 ppm	39	0/20
2500 ppm	78	0/20
5000 ppm	155	0/21
10,000 ppm	312.5	6/21
20,000 ppm	625	19/21
40,000 ppm	ND	8/20

Human $q_1^* = 1.57 \times 10^{-3}$ $(mg/kg/day)^{-1}$

ND = Not determined